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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,015	12/02/2003	Andrew Geall	1530.0610001/EJH/UWJ	3181

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,015	GEALL ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-11 and 18-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23-27* is/are allowed.

6)☒ Claim(s) *1, 6-11, 18-21, and 28-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 7/6/07. Claims 2-5 and 12-17 were canceled, and claims 28-42 were added.

Claims 1, 6-11, and 18-42 are pending and under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-11, 18-22 and 28-42 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6-11, 18-22 and 28-42 are indefinite in their recitation of "raising the temperature of the mixture above and below the cloud point". It is clear what is intended by "raising the temperature of the mixture above... the cloud point". However, it is unclear what is intended by "raising the temperature of the mixture... below the cloud point".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-8, 10, 11, and 18-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (WO 02/00844) in view of Hunter et al (US Patent 5,811,088).

Evans taught methods of formulating DNA vaccines by mixing a cationic surfactant such as benzalkonium chloride (BAK), a polyoxypropylene (POP)-polyoxyethylene (POE) copolymer such as CRL 1005, and a polynucleotide at a temperature below the cloud point of the copolymer (about 2-7°C). See paragraph bridging pages 32 and 33. The concentration ranges of nucleic acid, copolymer, and cationic surfactant are preferably in the ranges of 0.5-7.5 mg/ml, 1-70 mg/ml, and 0.1-10 mM, respectively (see page 21, line 32 to page 22, line 8.

Evans did not teach cold-filtering the mixture to produce a sterile formulation. However, it would have been obvious to one of ordinary skill in the art at the time of the invention that the formulations of Evans, intended for use as vaccines, should be sterile. Moreover, Hunter taught that solutions comprising poloxamers can be sterilized by passage through a 0.22 micron filter at a cold temperature at which they are soluble. See column 18, lines 40-45. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to cold filter formulations containing poloxamers at a temperature at which they are soluble, i.e. below their cloud point.

Because the instant claims are amended to exclude "raising the temperature of the mixture above and below the cloud point of said block copolymer", the question arises as to whether or not the cold filtration step should be taken prior to any increase

in temperature above the cloud point. MPEP 2144.04 (IV(C)) indicates that the rearrangement of steps is *prima facie* obvious unless it can be shown that the rearrangement results in new or unexpected results. So absent unexpected results, it would have been prima facie obvious to one of ordinary skill at the time of the invention to sterilize the mixture of Evans prior to any increase in temperature above the cloud point. Moreover, it would clearly save time and materials to sterilize the nucleic acid, copolymer, and cationic surfactant after they had been mixed, rather than separately and individually prior to mixing. So filtration of the mixture is considered obvious to one of ordinary skill in the art at the time of the invention and could have been carried out at any time in the procedure. Thus the invention as a whole was prima facie obvious.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (WO 02/00844), and Hunter et al (US Patent 5,811,088) as applied to claims 1, 6-8, 10, 11, and 18-22 above, and further in view of Emanuele et al (US Patent 6,933,286).

The teachings of Evans and Hunter are set forth above and render obvious methods of formulating nucleic acids with POP-POE copolymers and cationic surfactants, and sterilizing the mixtures by cold filtration. In addition to the use of POE-POP-POE copolymers such as CRL 1005, Evans also taught the use of PLURONIC R copolymers, which have the general organization POP-POE-POP required by instant claim 9. See page 22, line 20 or Evans.

Evans did not teach a POP-POE-POP copolymer wherein POP accounted for up to 20 kDa of the mass of the copolymer, and POE represented between 1 and 50% of the copolymer by weight.

Emanuele taught formulations comprising POP-POE-POP copolymers and nucleic acids for delivery to animals. The POP portion accounted for up to 20 kDa of the mass of the copolymer and the POE portion represented from 1-90% of the copolymer by weight. In one embodiment POP was 2500 Da and POE was 10% of the copolymer mass. See the claims especially claims 1-5 and 8-12.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the copolymer of Emanuele in the method of Evans as modified by Hunter. One would have been motivated to do so because Evans suggested the use of POP-POE-POP copolymers, and Emanuele taught that when making nucleic acid/POP-POE-POP copolymer complexes for in vivo delivery one should use copolymers wherein POP accounted for up to 20 kDa of the mass of the copolymer and POE represented from 1-90% of the copolymer by weight. Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 7/6/07 have been fully considered but they are not persuasive.

Applicant argues at pages 10 and 11 of the response that Evans requires that the block copolymer, cationic surfactant, and polynucleotide mixture must be raised above

the cloud point at least once. For support, Applicant relies on Evans at page 3, lines 6-11 which state "[t]he inclusion of the cationic surfactant results in an increased percentage of polynucleotide that is physically associated with the block copolymer/cationic surfactant upon mixing and/or temperature cycling through the block copolymer cloud point, thus resulting in an enhanced in vivo immune response to polynucleotide vaccines and/or gene therapy-based transgenes." Applicant states that the phrase mixing and/or temperature cycling through the block copolymer cloud point" can be interpreted in one of three ways: (a) mixing through the cloud point, (b) temperature cycling through the cloud point, and (c) mixing and temperature cycling through the cloud point. This issue is immaterial to the rejection of the claims as amended. The only issue is whether or not it would have been obvious to sterilize the mixture prior to any increase in temperature after mixing. As discussed above, absent new or unexpected results, it would be prima facie obvious to sterilize at any step in the procedure. Moreover, the teachings of Hunter indicate the advisability of performing cold sterilization of solutions containing poloxamers at temperatures below their cloud point.

Applicant argues that Evans does not teach any method in which the mixture is not ultimately warmed to a temperature above cloud point, as in Example 1. However, it is important to note that the particles in Example 1 were thawed to a temperature above the cloud point in part to determine the effect of warming rate on particle size (see page 34, lines 21-26). This is of interest to those of ordinary skill because the complexes are intended to be used for DNA delivery to cells and organisms, and so must ultimately be

warmed to a temperature above the cloud point of the block copolymer at the time of use. For this reason it was important to determine the effect of warming on particle size. This assay need not be performed as a part of producing a sterile mixture, so it would be obvious to practice the steps of the method without it.

Also, Evans stated that "[t]he inclusion of the cationic surfactant results in an increased percentage of polynucleotide that is physically associated with the block copolymer/cationic surfactant upon mixing and/or temperature cycling through the block copolymer cloud point, thus resulting in an enhanced in vivo immune response to polynucleotide vaccines and/or gene therapy-based transgenes." See page 3, lines 6-11. It follows that the step of raising the temperature through the cloud point could be performed at any time after mixing the components of the composition, including after a sterilization step.

Applicant argues in the paragraph bridging pages 12 and 13 that Evans teaches away from the claimed invention because Evans teaches that combination of BAK and DNA forms complexes and precipitates that are too large to filter, so DNA and a cationic surfactant would have to be filtered separately. Applicant relies on WO 99/21591 for support. This reference taught that DNA/BAK mixtures formed snowy, flocculent precipitates at BAK concentrations of above 0.04% w/v. Applicant's argument is unpersuasive because Evans taught that surfactants such as BAK should be used at a concentration of 0.1-10 mM which is below the threshold for precipitate formation cited in WO 99/21591. The molecular weight of BAK is 471.5, so the range of 0.1-10 mM corresponds to a w/v concentration range of 0.0047-0.047%. So the concentration

range contemplated by Evans is almost completely below the 0.04% precipitation threshold observed in WO 99/21591. Note that at BAK concentrations of 0.01 and 0.04, vesicular DNA/BAK complexes were formed in the size range of 50-400 nm. See '591 at page 33, lines 1-9. Applicant has presented no evidence that 50-400 nm vesicles cannot be cold filtered. Accordingly, Evans does not teach away from the claimed invention.

At pages 13 and 14 of the response, Applicant argues that obviousness cannot be predicated on what is not known at the time an invention is made, and cites an (Evans (2004) article that states that it was unexpected that DNA-BAK precipitates do not coexist with CRL1005-BAK-DNA particles in formulations above the cloud point of CRL1005. The relevance of this disclosure is unclear because the existence of precipitates above the cloud point has no bearing on whether or not it would be obvious to filter the mixture of Evans (WO 02/00844) at a temperature below the cloud point and prior to raising the temperature of the mixture.

Applicant argues that it would not be obvious to make a sterile solution by filtering the mixture of Evans (2004) below the cloud point because Evans taught that "Preparation of sterile vaccine formulations requires only the addition of sterile BAK to a solution of DNA/CRLI005 that is sterile-filtered below the cloud point." This is unpersuasive because the statement of Evans (2004) does not mean that any other order of event is not a viable and obvious alternative. Furthermore, the teachings of Evans in 2004 have no bearing on what one of ordinary skill in the art at the time of filing would have believed regarding obviousness.

Applicant argues at page 14 that one of ordinary skill at the time of the invention would not have been motivated to combine the teachings of Hunter and Evans because at that time it was not known that a combination of DNA-BAK in the presence of a copolymer does not form BAK-DNA precipitates. This is unpersuasive because, as discussed above, Applicant has failed to show that BAK-DNA precipitates (vesicles of 50-400 nm) are not cold-filterable.

Finally, Applicant subsequent argues that the discovery that the combination of polynucleotide, cationic surfactant, and copolymer mixture can be filtered is unexpected because it was not known that DNA and a cationic surfactant mixture does not form a precipitate in this combination. This is unpersuasive because Applicant has not met the burden of establishing unexpected results. MPEP 716.02(b) indicates that evidence relied upon to establish unexpected results should establish that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. In this case, the significance of the results is unclear because Applicant has provided no evidence that one of ordinary skill would not have been able to sterilize by cold filtration particles of 50-400 nm in size, i.e. the size particles expected when incubating BAK with DNA. Therefore Applicant has failed to show that one of ordinary skill would not have been motivated to cold filter mixtures of BAK, CL1005, and DNA. Moreover, MPEP 716.02(d) indicates that whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. In other words, the showing of unexpected results must

be reviewed to see if the results occur over the entire claimed range. In this case none of the claims is limited to mixtures of CL1005, BAK, and DNA, and it is not clear that similar results would be expected over the entire claimed range of cationic surfactants, POE/POP copolymers, and polynucleotides.

Conclusion

Claims 23-27 are allowable.

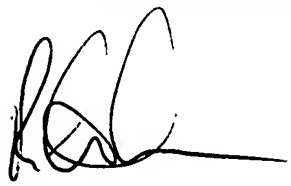
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635